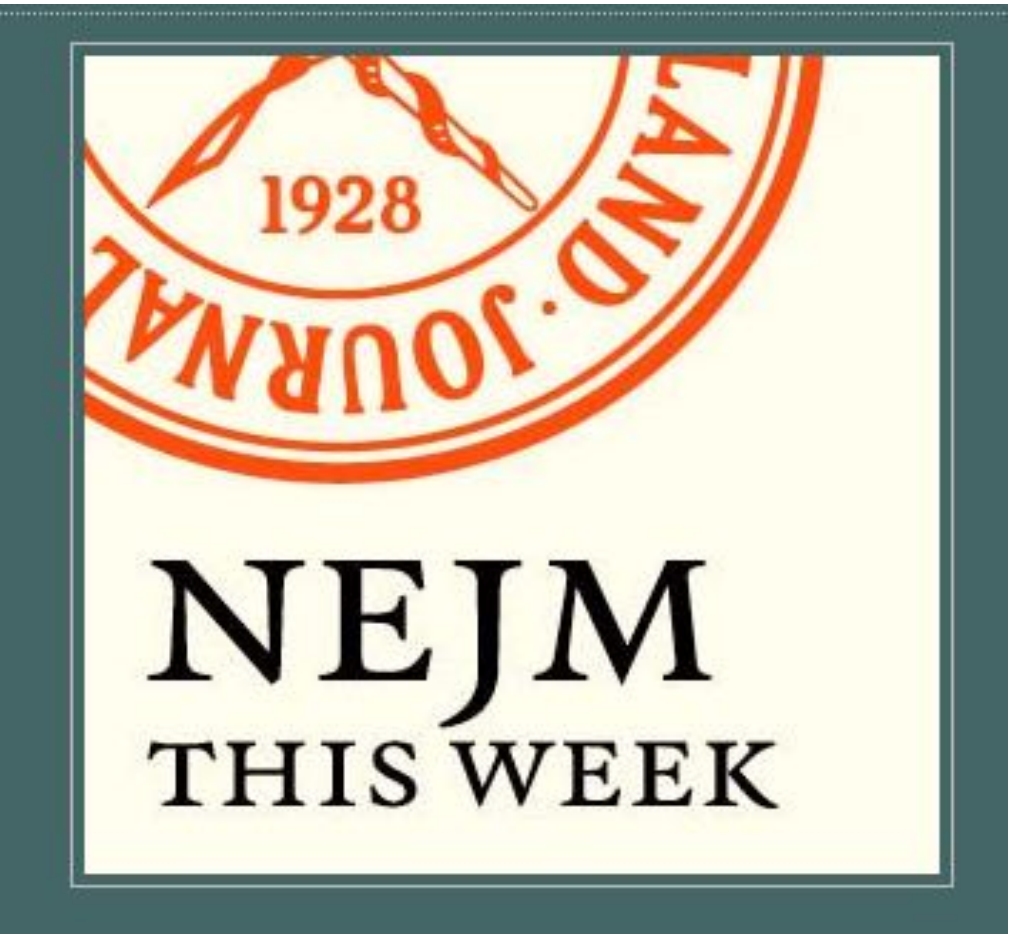
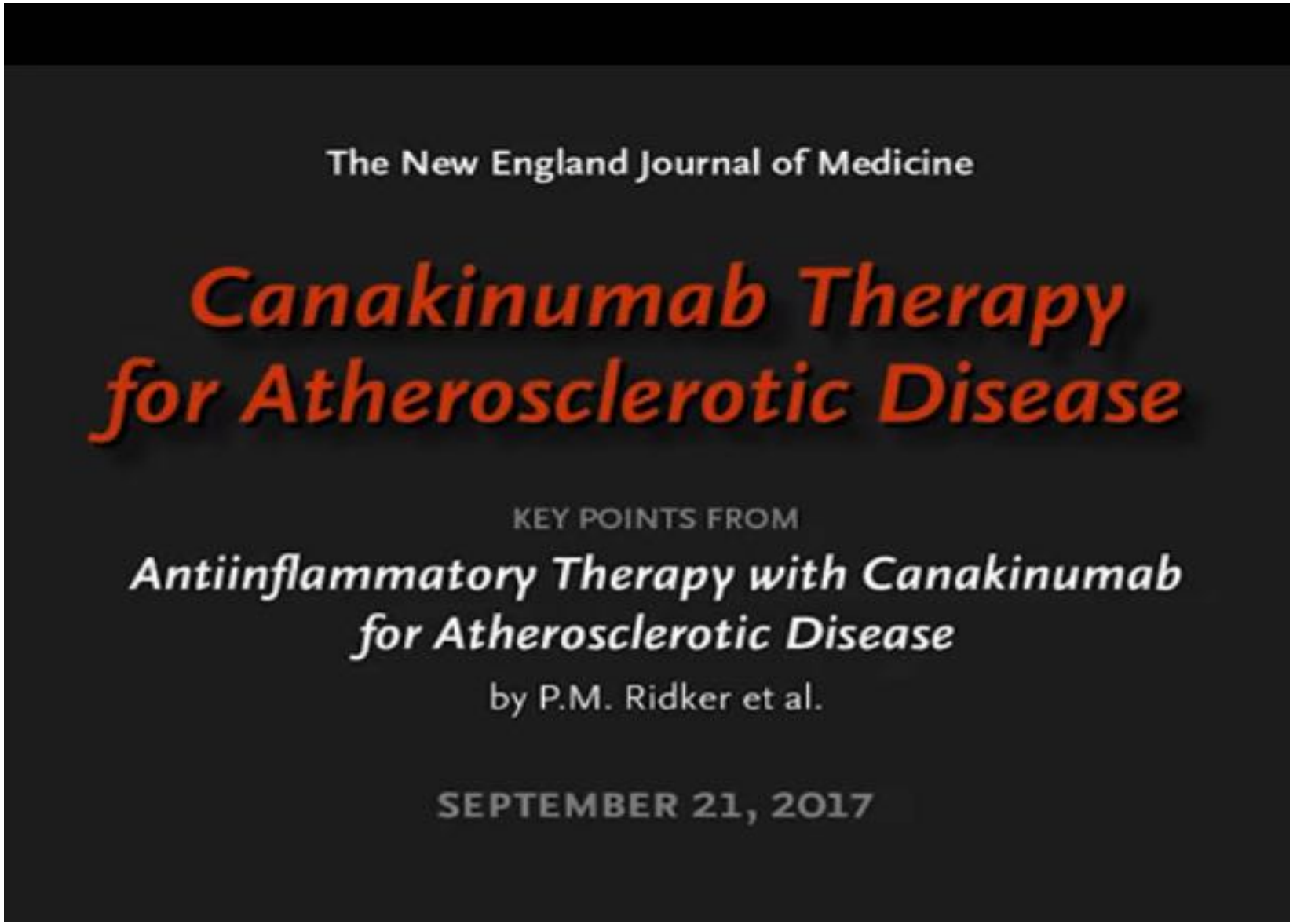


Noviembre 2019
Luis Quiroga Prado
INTERNISTA

- Regresion Aterosclerosis
- Prevencion secundaria enf Coronaria estable
- Prevencion secundaria enf Coronaria aguda
- FA Tratamiento con Ablaci
- Tratamiento Fibrosis pulmonar Nintenadib



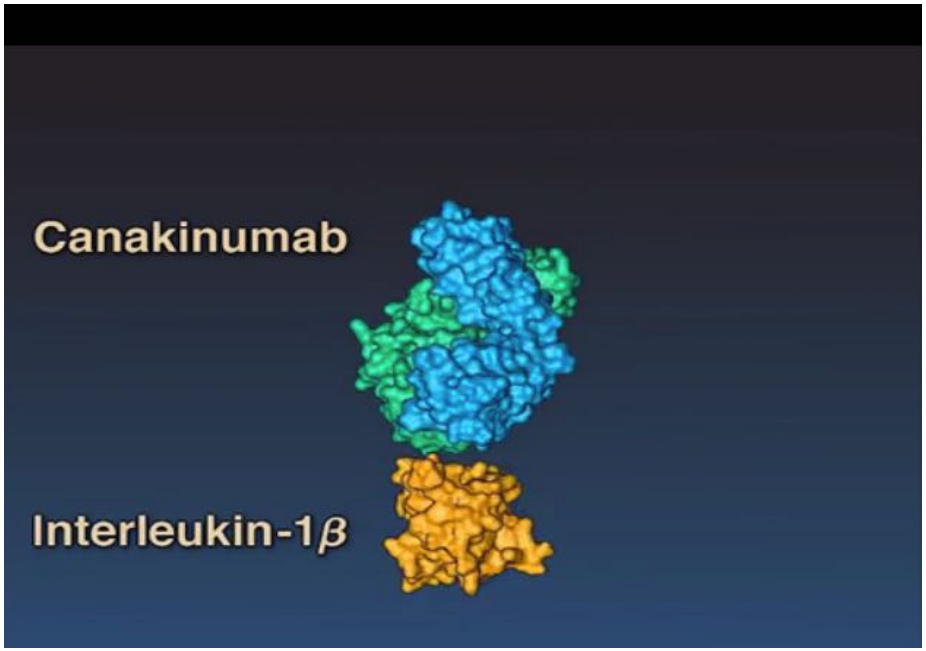
Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS)

BACKGROUND

- Experimental and clinical data* suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease.

- Canakinumab is approved for chronic idiopatic juvenile arthritis and criopiridine syndroms

*JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin



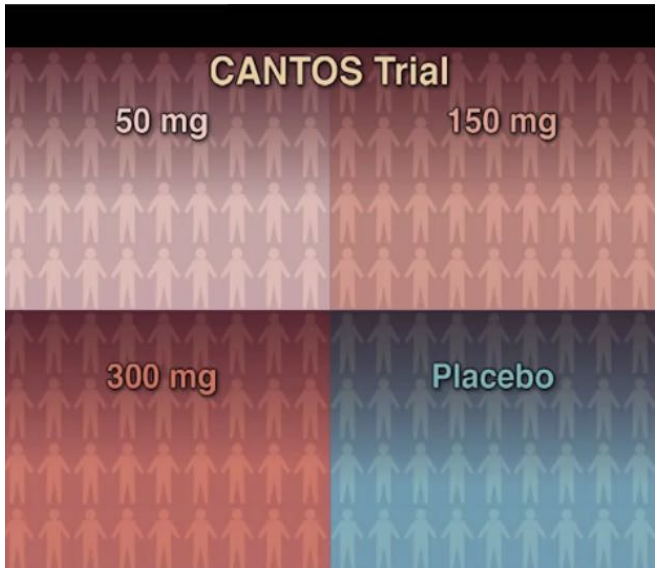
Yet, the inflammatory hypothesis of atherothrombosis has remained unproved

METHODS

- Randomized, Multicentric: 39 countries , double-blind trial
- N:10,061 patients
- Patients eligible
  - history of myocardial infarction
  - high-sensitivity C-reactive protein >= 2 mg (despite the use of aggressive secondary prevention strategies)

- three doses of canakinumab SC every 3 months

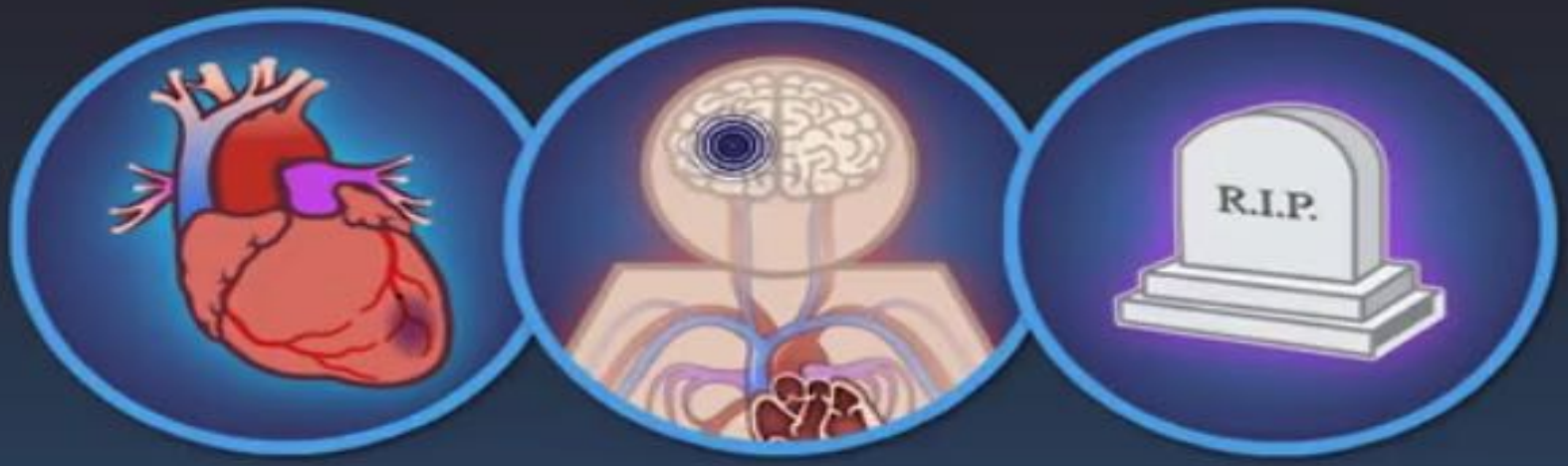
  50 mg 150 mg 300 mg,



RCT (sponsored by Novartis).

Methods II: 5 years of surveillance

MACE 3



first occurrence of nonfatal myocardial infarction

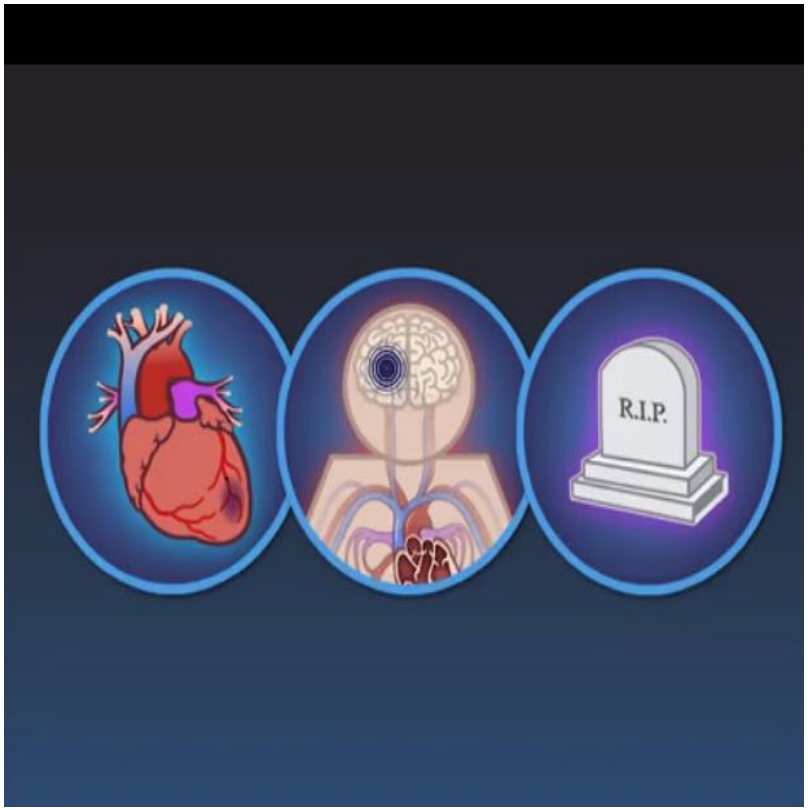
nonfatal stroke

cardiovascular death

statistical significance for the primary end point (the two-sided P value thresholds:
P < 0.01058 for the test of the 300-mg dose of canakinumab
P< 0.02115 for the tests of the other two doses

Methods II

- The second key secondary end point:
  - new-onset type 2 diabetes among patients with prediabetes
- Other prespecified secondary end points:
  - death from any cause and the composite of non- fatal myocardial infarction, any nonfatal stroke, or death from any cause.



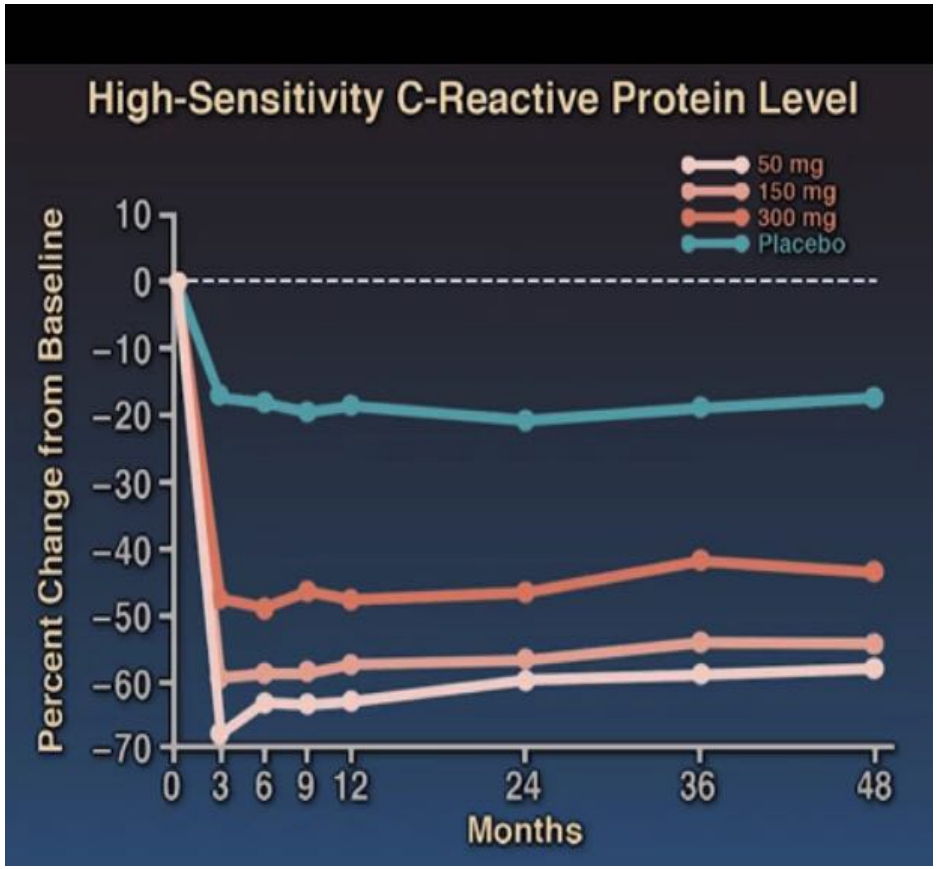
statistical significance for the primary end point (the two-sided P value thresholds:
P < 0.01058 for the test of the 300-mg dose of canakinumab
P< 0.02115 for the tests of the other two doses

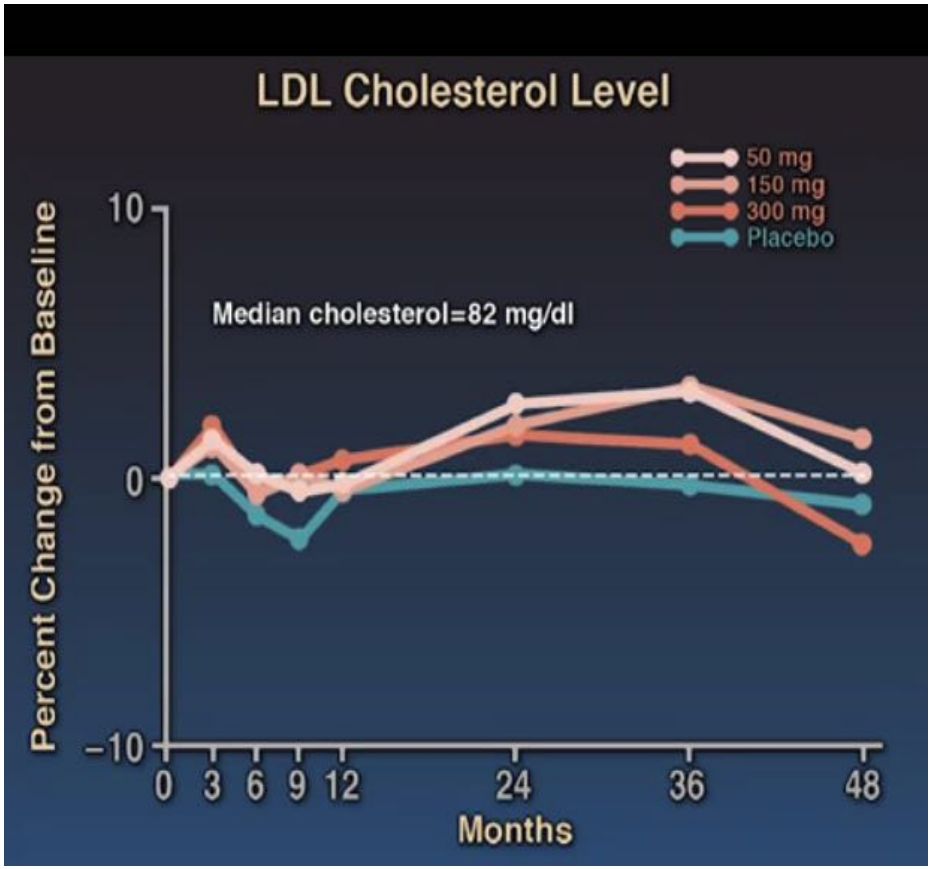
Basal Characteristic

Patients had an average age of 61 years, had multiple cardiac risk factors, and had a history of frequent revascularization and aggressive use of secondary prevention medications, including approximately 90% of the patients being treated with a statin.

		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)
Age — yr	61.1±10.0	61.1±10.1	61.2±10.0	61.1±10.1	61.1±10.1
Female sex — no. (%)	865 (25.9)	541 (24.9)	575 (25.2)	606 (26.8)	1722 (25.6)
Current smoking — no. (%)	765 (22.9)	531 (24.5)	534 (23.4)	536 (23.7)	1601 (23.8)
Median body-mass index (IQR)	29.7 (26.6–33.8)	29.9 (26.6–33.9)	29.8 (26.5–33.7)	29.8 (26.5–33.8)	29.9 (26.6–33.8)
Hypertension — no. (%)	2644 (79.1)	1751 (80.7)	1814 (79.4)	1799 (79.5)	5364 (79.9)
Diabetes — no. (%)	1333 (39.9)	854 (39.4)	954 (41.8)	888 (39.2)	2696 (40.1)
Qualifying myocardial infarction — no. (%)					
STEMI	1807 (54.0)	1231 (56.7)	1231 (53.9)	1213 (53.6)	3675 (54.7)
Non-STEMI	1132 (33.9)	710 (32.7)	781 (34.2)	761 (33.6)	2252 (33.5)
Unknown type or missing data	405 (12.1)	229 (10.6)	272 (11.9)	289 (12.8)	790 (11.8)
History of PCI — no. (%)	2192 (65.6)	1454 (67.0)	1555 (68.1)†	1509 (66.7)	4518 (67.3)
History of CABG — no. (%)	469 (14.0)	302 (13.9)	324 (14.2)	316 (14.0)	942 (14.0)
History of congestive heart failure — no. (%)	721 (21.6)	451 (20.8)	478 (20.9)	523 (23.1)	1452 (21.6)
Lipid-lowering therapy — no./total no. (%)	3132/3344 (93.7)	2038/2169 (94.0)	2114/2280 (92.7)	2113/2259 (93.5)	6265/6708 (93.4)
Statin — no./total no. (%)	3045/3344 (91.1)	1990/2169 (91.7)	2065/2280 (90.6)	2057/2259 (91.1)	6112/6708 (91.1)
Renin–angiotensin inhibitor — no./total no. (%)	2665/3338 (79.8)	1718/2166 (79.3)	1817/2277 (79.8)	1792/2250 (79.6)	5327/6693 (79.6)
Anti-ischemia agent — no./total no. (%)‡	3080/3344 (92.1)	1974/2169 (91.0)	2079/2280 (91.2)	2058/2259 (91.1)	6111/6708 (91.1)
Antithrombotic agent or anticoagulant — no./total no. (%)	3188/3344 (95.3)	2059/2169 (94.9)	2157/2280 (94.6)	2149/2259 (95.1)	6365/6708 (94.9)
Median high-sensitivity CRP level (IQR) — mg/liter	4.10 (2.75–6.85)	4.25 (2.80–7.15)	4.25 (2.85–7.05)	4.15 (2.85–7.15)	4.20 (2.80–7.10)
Median interleukin-6 level (IQR) — ng/liter	2.61 (1.80–4.06)	2.53 (1.80–4.17)	2.56 (1.74–4.11)	2.59 (1.79–4.08)	2.56 (1.77–4.13)
Median total cholesterol level (IQR) — mg/dl	161 (137–190)	159 (136–189)	159 (136–188)	161 (137–189)	160 (136–189)
Median LDL cholesterol level (IQR) — mg/dl	82.8 (64.2–107.5)	81.2 (62.3–106.0)	82.4 (63.4–106.0)	83.5 (64.0–108.0)	82.0 (63.0–106.7)
Median HDL cholesterol level (IQR) — mg/dl	44.5 (37.1–52.6)	43.7 (37.0–52.2)	43.7 (36.3–52.0)†	44.0 (36.7–53.0)	43.7 (36.7–52.2)†
Median triglyceride level (IQR) — mg/dl	139 (100–194)	140 (102–198)	139 (101–196)	138 (103–194)	139 (102–196)

Resultados





Discontinued by the end of follow-up:

18.1% in the placebo group

18.7% in the combined canakinumab groups

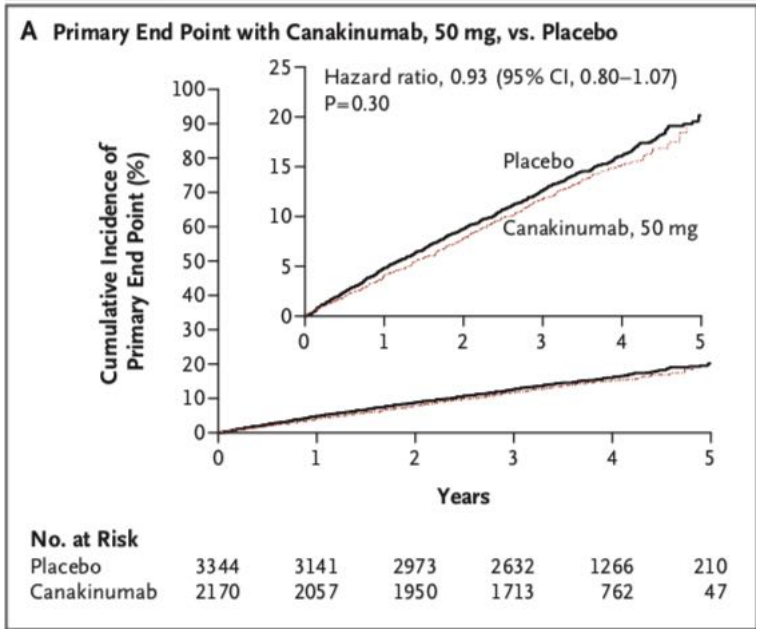
Results over endpoints

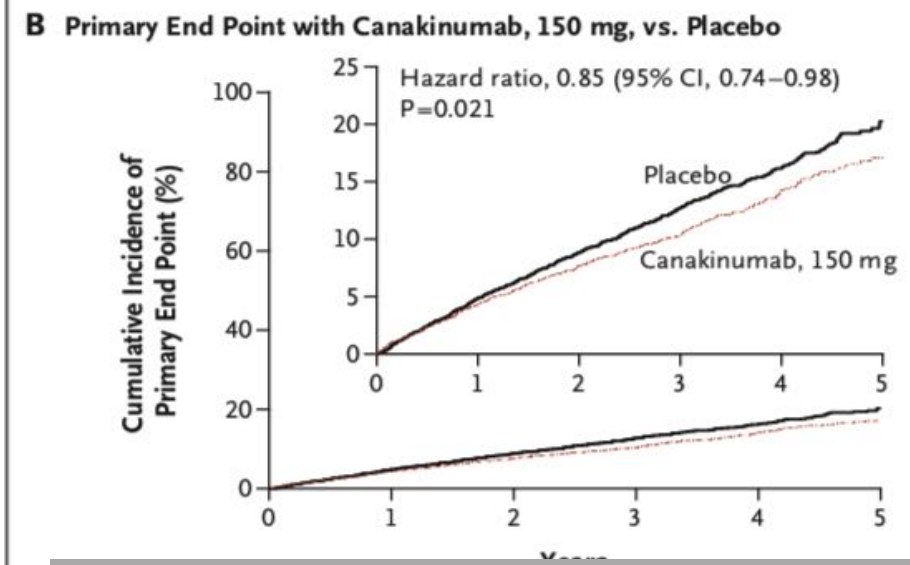
Table 2. Incidence Rates and Hazard Ratios for Major Clinical Outcomes and All-Cause Mortality.*

Clinical Outcome	Placebo Group (N=3344)	Canakinumab				P Value for Trend across Doses vs. Placebo
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)	
Primary end point†						
Incidence rate per 100 person-yr (no. of patients)	4.50 (535)	4.11 (313)	3.86 (320)	3.90 (322)	3.95 (955)	0.02
Hazard ratio (95% CI)	1.00	0.93 (0.80–1.07)	0.85 (0.74–0.98)	0.86 (0.75–0.99)	0.88 (0.79–0.97)	
P value	—	0.30‡	0.021§	0.031‡	0.02	
Key secondary cardiovascular end point¶						
Incidence rate per 100 person-yr (no. of patients)	5.13 (601)	4.56 (344)	4.29 (352)	4.25 (348)	4.36 (1044)	0.003
Hazard ratio (95% CI)	1.00	0.90 (0.78–1.03)	0.83 (0.73–0.95)	0.83 (0.72–0.94)	0.85 (0.77–0.94)	
P value	—	0.12‖	0.005§	0.004‖	0.001	

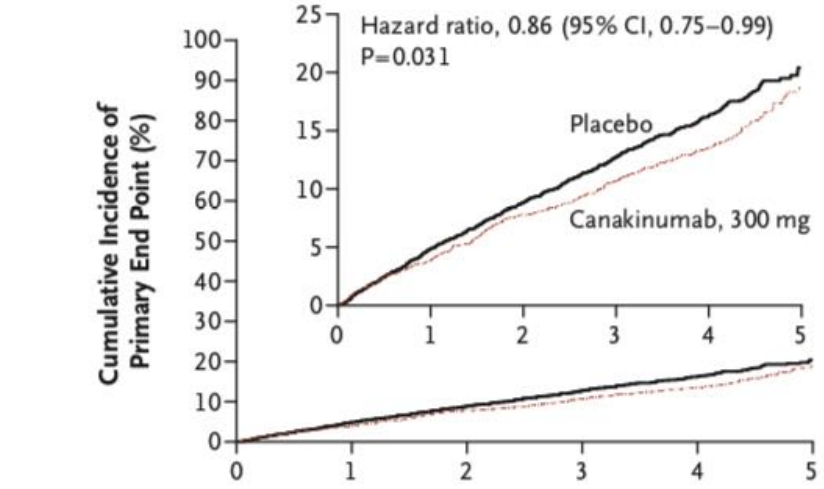
although the modest overall effect was completely driven by a lower incidence of myocardial infarction.

All-cause mortality was neutral in the comparison of all canakinumab doses with placebo (hazard ratio, 0.94; 95% confidence interval, 0.83 to 1.06; P=0.31).

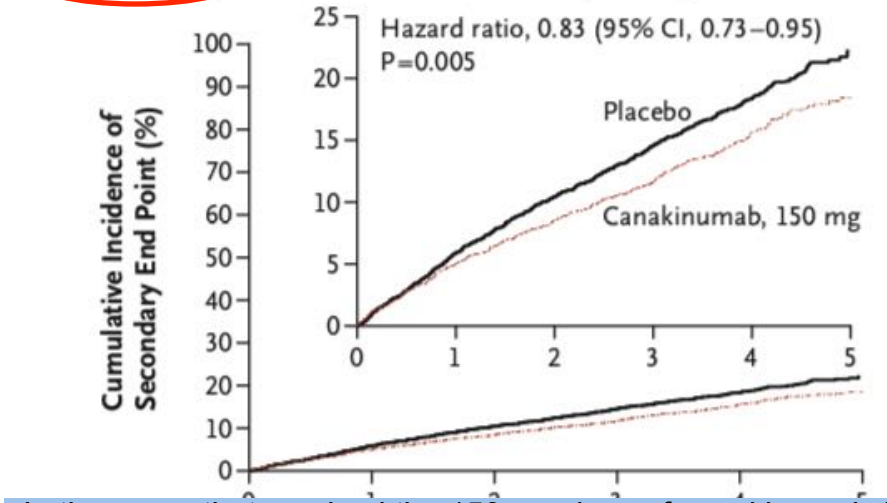




a significant effect for the primary end point was observed in the 150-mg group (hazard ratio vs. placebo, 0.85; P = 0.02075, with a thresh- old P value of 0.02115)



The effect of the 300-mg dose looked similar, but this dose level did not achieve statistical significance because of the complexities of testing multiple doses against placebo.



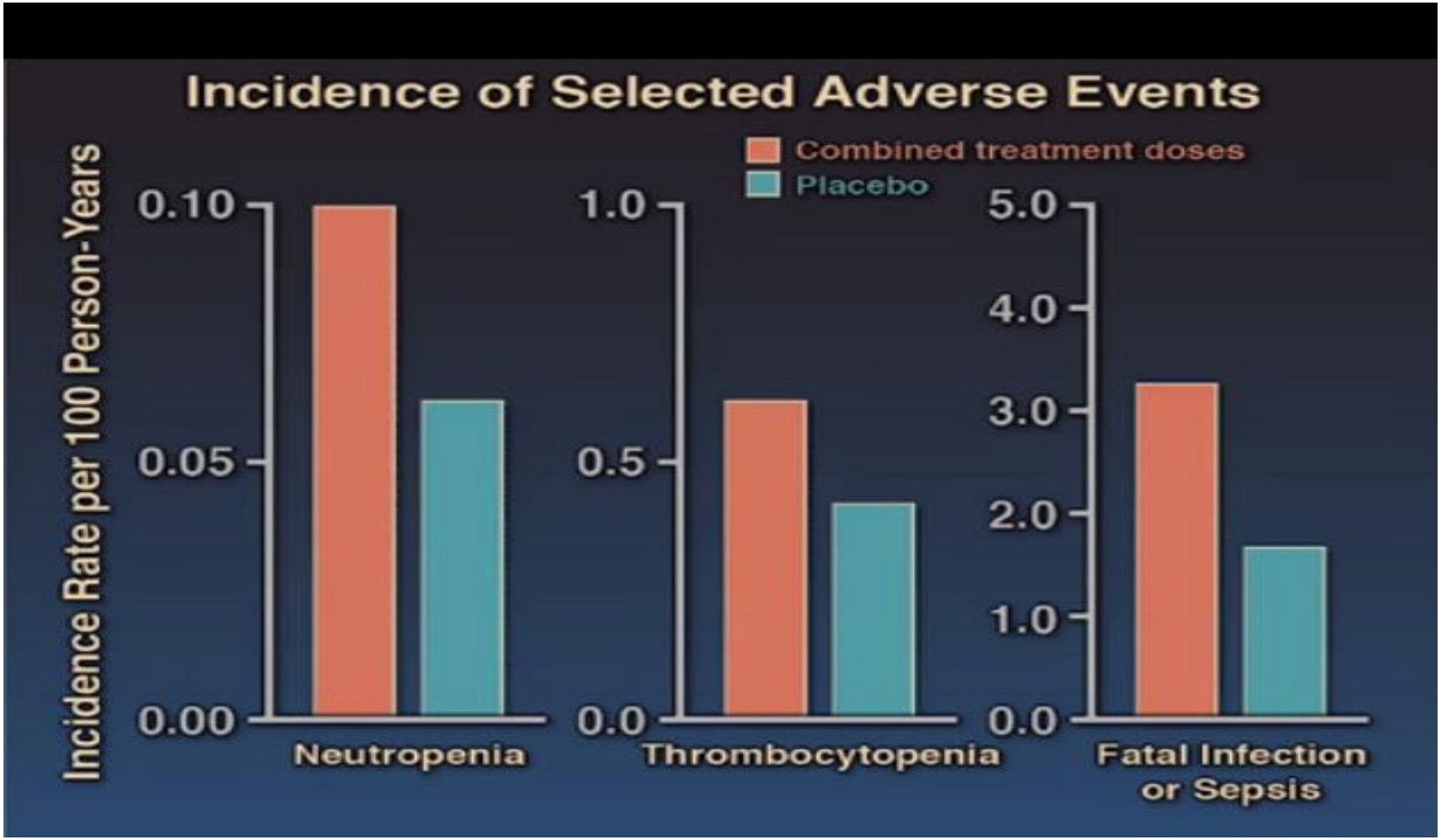
In the group that received the 150-mg dose of canakinumab (for which the P value met the significance threshold for the primary end point), the hazard ratio versus placebo for the secondary cardiovas- cular end point was 0.83 (P=0.00525, with a threshold P value of 0.00529)

Table 3. Incidence Rates and Numbers of Serious Adverse Events and Selected Safety Laboratory Data During Treatment, Stratified According to Trial Group.*

Adverse Event or Laboratory Variable	Placebo Group (N=3344)	Canakinumab				P Value	
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)	For Trend across Doses vs. Placebo	For Combined Dose Groups vs. Placebo
Event — incidence rate per 100 person-yr (no. of patients with event)							
Any serious adverse event	11.96 (1202)	11.41 (741)	11.71 (812)	12.33 (836)	11.82 (2389)	0.43	0.79
Any serious adverse event of infection	2.86 (342)	3.03 (230)	3.13 (258)	3.25 (265)	3.14 (753)	0.12	0.14
Cellulitis	0.24 (30)	0.24 (19)	0.37 (32)	0.41 (35)	0.34 (86)	0.02	0.09
Pneumonia	0.90 (112)	0.94 (74)	0.94 (80)	0.99 (84)	0.95 (238)	0.56	0.62
Urinary tract infection	0.22 (27)	0.18 (14)	0.24 (21)	0.20 (17)	0.21 (52)	0.84	0.87
Opportunistic infection†	0.18 (23)	0.16 (13)	0.15 (13)	0.20 (17)	0.17 (43)	0.97	0.78
Pseudomembranous colitis	0.03 (4)	0.13 (10)	0.05 (4)	0.12 (10)	0.10 (24)	0.13	0.03
Fatal infection or sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.02
Any cancer‡	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31	0.38
Fatal cancer‡	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	<0.001	0.02
Other adverse event							
Injection-site reaction†	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Arthritis	3.32 (385)	2.15 (164)	2.17 (180)	2.47 (201)	2.26 (545)	0.002	<0.001
Osteoarthritis	1.67 (202)	1.21 (94)	1.12 (95)	1.30 (109)	1.21 (298)	0.04	<0.001
Gout	0.80 (99)	0.43 (34)	0.35 (30)	0.37 (32)	0.38 (96)	<0.001	<0.001
Drug-induced liver injury†	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.004	0.05
Leukopenia	0.24 (30)	0.30 (24)	0.37 (32)	0.52 (44)	0.40 (100)	0.002	0.01
Neutropenia	0.06 (7)	0.05 (4)	0.07 (6)	0.18 (15)	0.10 (25)	0.01	0.17
Any hemorrhage	4.01 (462)	3.33 (249)	4.15 (327)	3.82 (301)	3.78 (877)	0.94	0.31
Thrombocytopenia	0.43 (53)	0.56 (44)	0.54 (46)	0.71 (60)	0.60 (150)	0.02	0.03
Hepatic variable — percent of patients with condition (no.)							
Alanine aminotransferase >3× normal value	1.4 (46)	1.9 (42)	1.9 (44)	2.0 (45)	2.0 (131)	0.19	0.06
Aspartate aminotransferase >3× normal value	1.1 (36)	1.5 (32)	1.5 (35)	1.5 (34)	1.5 (101)	0.30	0.11
Alkaline phosphatase >3× normal value	0.4 (15)	0.5 (11)	0.4 (10)	0.5 (12)	0.5 (33)	0.67	0.82
Bilirubin >2× normal value	0.8 (26)	1.0 (21)	0.7 (15)	0.7 (15)	0.8 (51)	0.34	0.83

We found a significantly higher incidence of fatal infection and sepsis with canakinumab than with placebo, as well as a reduction in platelet counts with no increase in bleeding risk. By contrast, cancer mortality was significantly lower

Efectos adversos



Conclusions

Treatmente with Canakinumab In patients with cardiovascular disease and residual inflammatory risk (PCR hs > 2 mg) despite vigorous treatment with statin,

- significantly reduced high-sensitivity C-reactive protein levels without reducing the LDL cholesterol level
- The 150-mg dose resulted in a significantly lower incidence of recurrent cardiovascular events than placebo.

Critics CANTOS study

- Dessing:
  - Decresed sample from 17,200 patients, to 10,000.
  - Prolongation the follow-up to allow for the accumulation of an adequate number of events
  - Introduction of a group for 50 mg kanakinumab;
- Modest benefical effect was about reduction in miocardial infarction.
  - More information is needed about the details (infarct size, Q-wave vs. non–Q-wave, and spontaneous or procedure-related).
- No reduction in mortality
- Concern about safety profile
- Considerations about canakinumab cost: Given monthly for approved indications, canakinumab is priced at approximately $200,000 per year in the United States

First evidence about the inflammatory hypothesis of coronary artery disease as therapeutic target

ORIGINAL ARTICLE

Low-Dose Methotrexate for the Prevention of Atherosclerotic Events

Paul M Ridker, M.D., Brendan M. Everett, M.D., Aruna Pradhan, M.D., Jean G. MacFadyen, B.A., Daniel H. Solomon, M.D., Elaine Zaharris, B.A., Virak Mam, B.S., Ahmed Hasan, M.D., Yves Rosenberg, M.D., Erin Iturriaga, M.S.N., Milan Gupta, M.D., Michelle Tsigoulis, Subodh Verma, M.D., Michael Clearfield, D.O., Peter Libby, M.D., Samuel Z. Goldhaber, M.D., Roger Seagle, M.D., Cyril Ofori, M.D., Mohammad Saklayen, M.D., Samuel Butman, M.D., Narendra Singh, M.D., Michel Le May, M.D., Olivier Bertrand, M.D., James Johnston, M.D., Nina P. Paynter, Ph.D., and Robert J. Glynn, Sc.D., for the CIRT Investigators*

The Cardiovascular Inflammation Reduction Trial (CIRT)
U.S. National Heart, Lung, and Blood Institute (NHLBI).

Background

- Inflammation plays a critical role in atherothrombosis
- In the CANTOS study, treatment with canakinumab, a monoclonal antibody that selectively neutralizes interleukin-1β, resulted in fewer cardiovascular events than placebo, without lowering lipid levels or blood pressure
- These results thus provide proof of principle that inhibiting inflammation can prevent atherosclerotic events

Background

- We hypothesized an alternative approach to inhibition of inflammation with Methotrexate
  - low-dose methotrexate has antiinfamatory effect
  - Low-dose is widely used treatment for inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis
  - low-dose methotrexate use reduced vascular event rates in patients with rheumatoid arthritis or psoriatic arthritis
  - Low-dose methotrexate is an inexpensive

Methods I

- RCT NHLBI sponsored (budgeting nearly $80 million)
- N= 7000 to 5500:
  - for 530 to 634 events to give the trial 90% power to detect a 23% lower rate of the primary end point
- Inclusion criteria:
  - history of myocardial infarction or multivessel coronary disease and either type 2 diabetes or the metabolic syndrome in a medically stable condition
- Exclusion criteria similar to use of methotrexate in rheumatic diseases
- open-label run-in phase lasting 5 to 8 weeks:
  - 1 mg of oral folic acid daily, + oral methotrexate once weekly in doses increasing sequentially from 5 mg to 10 mg to 15 mg.
- Randomly assigned in a 1:1 ratio,
  - Placebo 2395 patients v methotrexate 2391 patients
  - At 4 months, the dose was increased, per protocol, to 20 mg of methotrexate (or matching placebo)

Methods II

Primary Endpoint al 4 years:

* Time to first major cardiovascular event
  -Composite of non-fatal MI, stroke and CV death

Secondary Endpoints

* All-cause mortality
* Percutaneous or surgical coronary revascularization
* Hospitalization for congestive heart failure
* Incident venous thromboebolism
* Incident atrial fibrillation
* Incident diabetes among those without diabetes at randomization
* Incident peripheral artery disease
* Clinically worsening aortic stenosis

Table 1. Baseline Characteristics of the Trial Participants.*

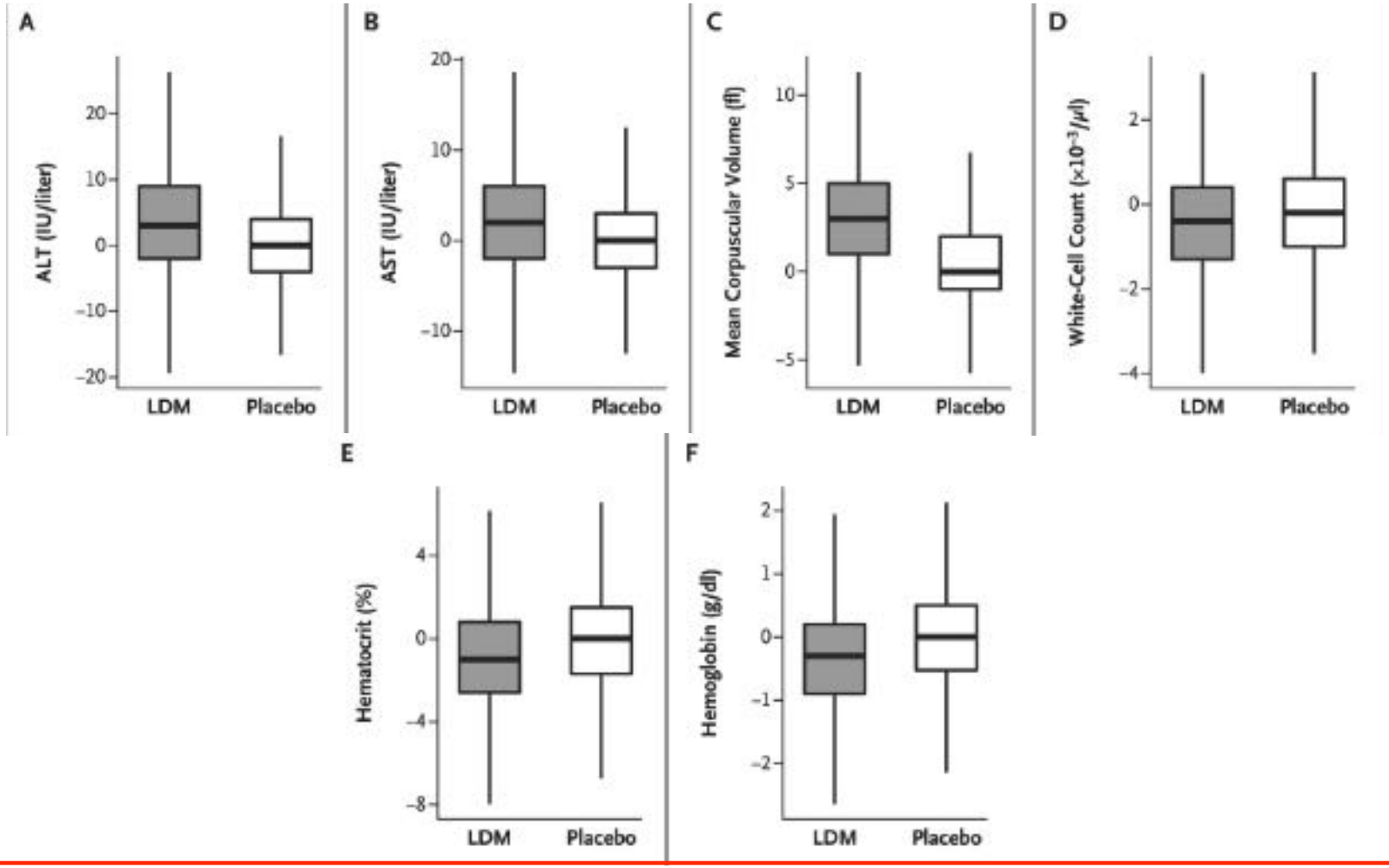
Characteristic	Low-Dose Methotrexate (N=2391)	Placebo (N=2395)
Median age (IQR) — yr	65.6 (59.7–71.8)	66.0 (59.8–71.7)
Female sex — no. (%)	461 (19.3)	437 (18.2)
Country — no. (%)		
Canada	407 (17.0)	404 (16.9)
United States	1984 (83.0)	1991 (83.1)
Nonwhite race or Hispanic ethnic group — no./total no. (%)†	545/2346 (23.2)	485/2322 (20.9)
Current smoker — no. (%)	267 (11.2)	270 (11.3)
Alcohol use — no. (%)		
Rarely or never	1487 (62.2)	1473 (61.5)
≤1 drink/wk	514 (21.5)	520 (21.7)
>1 drink/wk	390 (16.3)	402 (16.8)
Median body-mass index (IQR)‡	31.6 (28.2–35.5)	31.3 (28.1–35.6)
Hypertension — no. (%)	2153 (90.0)	2169 (90.6)
Qualifying event — no. (%)		
Myocardial infarction	1451 (60.7)	1458 (60.9)
Multivessel coronary disease	940 (39.3)	937 (39.1)
Qualifying coexisting condition — no. (%)		
Diabetes	788 (33.0)	823 (34.4)
Metabolic syndrome	771 (32.2)	780 (32.6)
Diabetes and metabolic syndrome	832 (34.8)	792 (33.1)
History of congestive heart failure	288 (12.0)	332 (13.9)
History of percutaneous coronary intervention	1396 (58.4)	1420 (59.3)
History of coronary artery bypass grafting	1010 (42.2)	1032 (43.1)

The median age of the patients was 66 years, 19% were women, and 22% identified themselves as nonwhite or Hispanic Previous myocardial infarction in 61% of the patients and multivessel coronary disease without previous infarction in 39%. Coexisting conditions were diabetes in 68% and the metabolic syndrome without diabetes in 32%.

Use of ACE inhibitor or ARB — no. (%)	1736 (72.6)	1724 (72.0)
Use of statin — no. (%)	2058 (86.1)	2052 (85.7)
Use of beta-blocker — no. (%)	1870 (78.2)	1905 (79.5)
Use of antiplatelet or antithrombotic agent — no. (%)	2082 (87.1)	2054 (85.8)
Median lipid levels (IQR) — mg/dl		
Total cholesterol	141.0 (122.0–168.0)	140.9 (122.0–164.0)
LDL cholesterol	68.0 (54.0–87.0)	68.0 (53.3–86.0)
HDL cholesterol	41.0 (34.7–49.0)	41.0 (35.0–48.0)
Triglycerides	135.4 (98.0–191.2)	136.0 (98.2–191.6)
Median high-sensitivity C-reactive protein level (IQR) — mg/liter	1.53 (0.78–3.59)	1.50 (0.70–3.29)
Median interleukin-1β level (IQR) — pg/ml	1.59 (0.49–3.17)	1.46 (0.53–3.11)
Median interleukin-6 level (IQR) — pg/ml	2.37 (1.53–3.76)	2.30 (1.58–3.51)
Median glycated hemoglobin level (IQR) — %	6.6 (6.0–7.5)	6.5 (5.9–7.5)

Results

- mean weekly dose:
  - 18.8 mg in the methotrexate group and 19.0 mg in the placebo group.
- Discontinued the trial regimen.
  - 21% of the patients in the methotrexate group and 22% in the placebo group



Increases ALT and AST
Increases mean corpuscular volume
Reductions in the total white-cell count
Reduction in hematocrit level, and hemoglobin level

(P<0.001 for all comparisons)

No reductions in levels of C-reactive protein, interleukin-1β, interleukin-6 or lipids

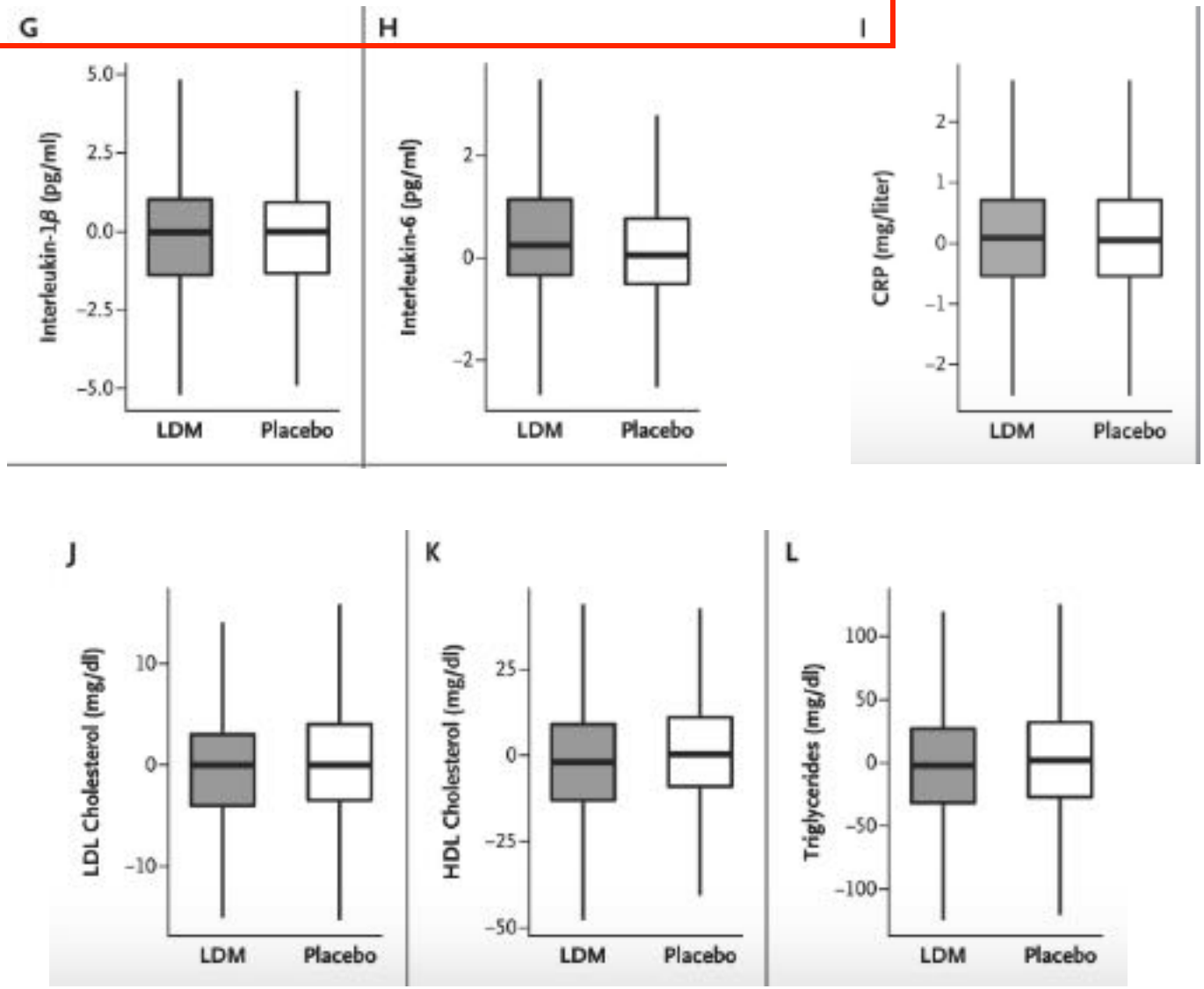
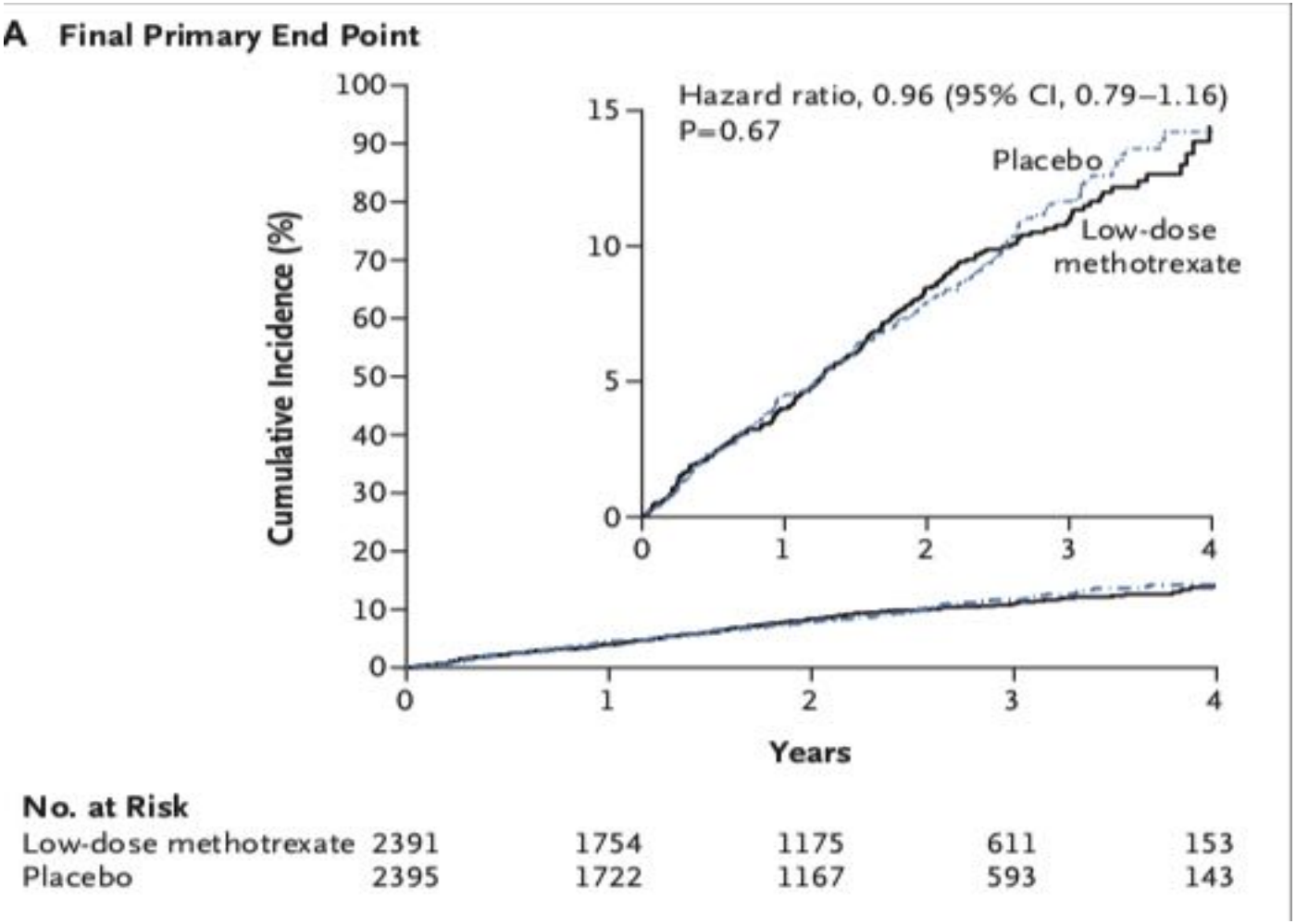


Table 2. Cardiovascular Clinical End Points.

End Point	Low-Dose Methotrexate (N=2391)		Placebo (N=2395)		Hazard Ratio (95% CI)*	P Value
	no. of patients	*incidence rate/ 100 person-yr*	*no. of patients*	*incidence rate/ 100 person-yr*		
Primary end points†						
Final primary end point: major adverse cardiovascular event or hospitalization for unstable angina that led to urgent revascularization	201	4.13	207	4.31	0.96 (0.79–1.16)	0.67
Original primary end point: major adverse cardiovascular event	170	3.46	167	3.43	1.01 (0.82–1.25)	0.91
Secondary end points†						
Death from any cause	96	1.80	83	1.55	1.16 (0.87–1.56)	
Major adverse cardiovascular event or any coronary revascularization	278	5.86	288	6.15	0.95 (0.81–1.12)	
Hospitalization for congestive heart failure	48	0.95	53	1.06	0.89 (0.60–1.31)	
Major adverse cardiovascular event, coronary revascularization, hospitalization for congestive heart failure, or death from any cause	344	7.30	345	7.42	0.98 (0.84–1.14)	
Tertiary end points						
Nonfatal myocardial infarction	113	2.29	114	2.32	0.99 (0.76–1.29)	
Nonfatal stroke	28	0.55	30	0.60	0.91 (0.54–1.52)	
Cardiovascular death	49	0.92	43	0.80	1.14 (0.76–1.72)	
Hospitalization for unstable angina that led to urgent revascularization	41	0.81	50	1.01	0.81 (0.53–1.22)	
Coronary revascularization	190	3.95	205	4.30	0.92 (0.75–1.12)	
Arterial revascularization	195	4.05	185	3.84	1.05 (0.86–1.28)	



It is thus possible that the ability of methotrexate to reduce the C-reactive protein level is limited to clinical situations in which inflammation levels are high

Adverse events

- Modest leukopenia and elevations of ALT and AST levels were more common in the methotrexate group
- Mouth sores and oral pain, unintended weight losswere more prevalent in the methotrexate group
- Cancers developed in more patients in the methotrexate group than in the placebo group (52 vs. 30; rate ratio, 1.72; P = 0.02)

- Bleeding and infection, were similar in the two

Conclusions: low-dose methotrexate antiinflamatory therapy

did not reduce

•interleukin-1β, interleukin-6, or high-sensitivity C-reactive protein

•cardiovascular events

(The inflamatory target in atheroclerosis may depend of others patways different of Inhibition of interleukin-1β–interleukin-6 signaling, a process initiated at the level of the NLRP3 inflammasome)

ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., et al.

BACKGROUND

Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS)

The Cardiovascular Inflammation Reduction Trial (CIRT)

…..the search for a widely used alternative anti-inflammatory treatment that may reduce the risk of atherosclerotic events among patients with coronary artery disease continues

autumn crocus

Mechanism of action:

inhibition of tubulin polymerization and microtubule generation
possibly, effects on cellular adhesion molecules, inflammatory chemokines, and the inflammasome.

Colchicine Cardiovascular Outcomes Trial (COLCOT)

METHODS

randomized, double-blind, placebo-controlled trial,
167 centers in the 12 countries

4745 Patients: were enrolled a mean of 13.5 days after M.I.

1:1 ratio to receive either colchicine (at a dose of 0.5 mg once daily) or placebo

The primary efficacy: MACE

- Death from cardiovascular causes
- Resuscitated cardiac arrest
- Myocardial infarction
- Stroke
- Urgent hospitalization for angina leading to coronary revascularization

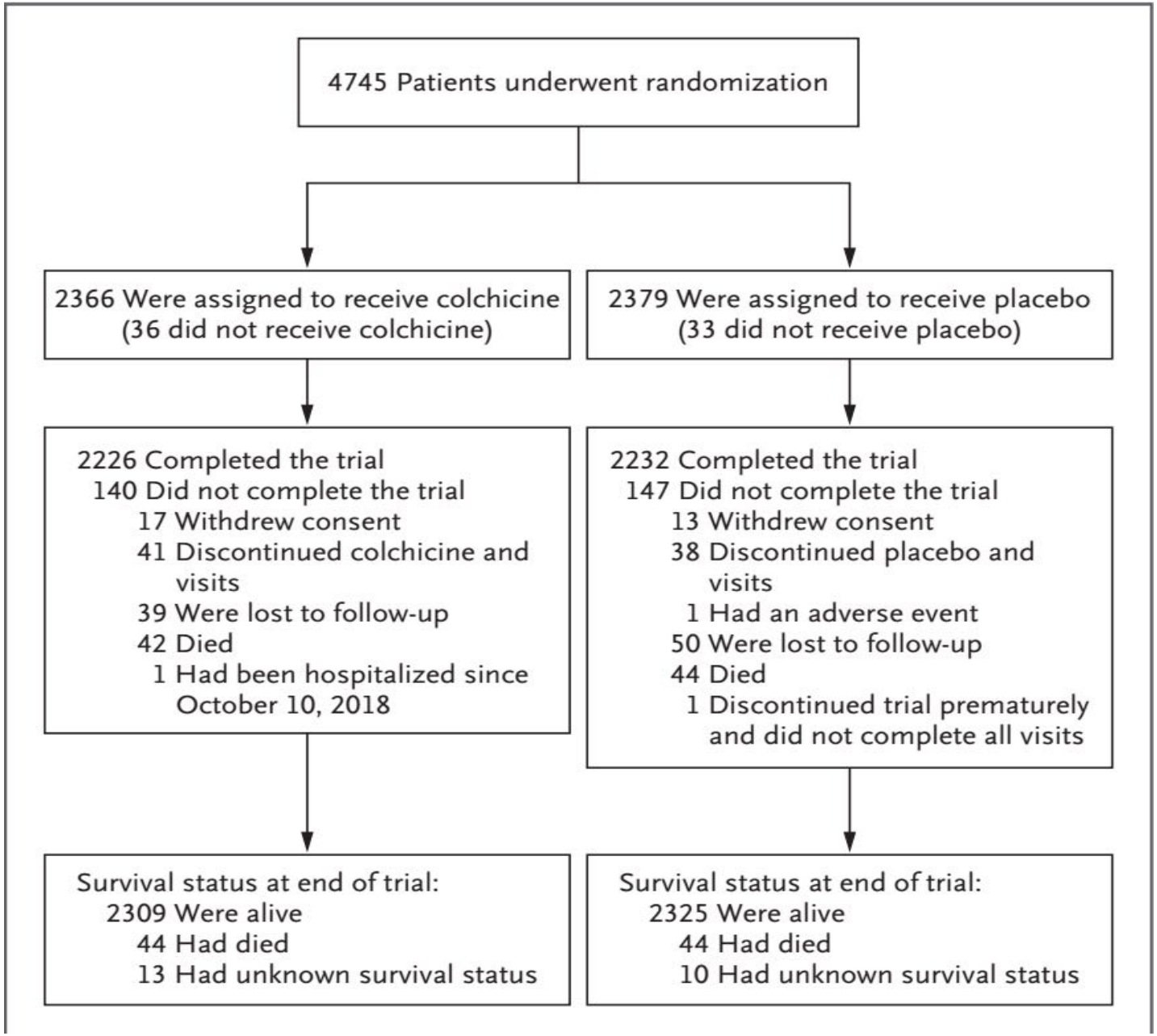


Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

The mean age 60.6 years 19.2% were women 20.2% had diabetes.
percutaneous revascularization procedures 93%
Dual antiplatelet therapy and statins in 98 and 99% respectively

RESULTS

followed for a median of 22.6 months.

event occurred:

5.5% of the patients in the colchicine group; 7.1% in the placebo group

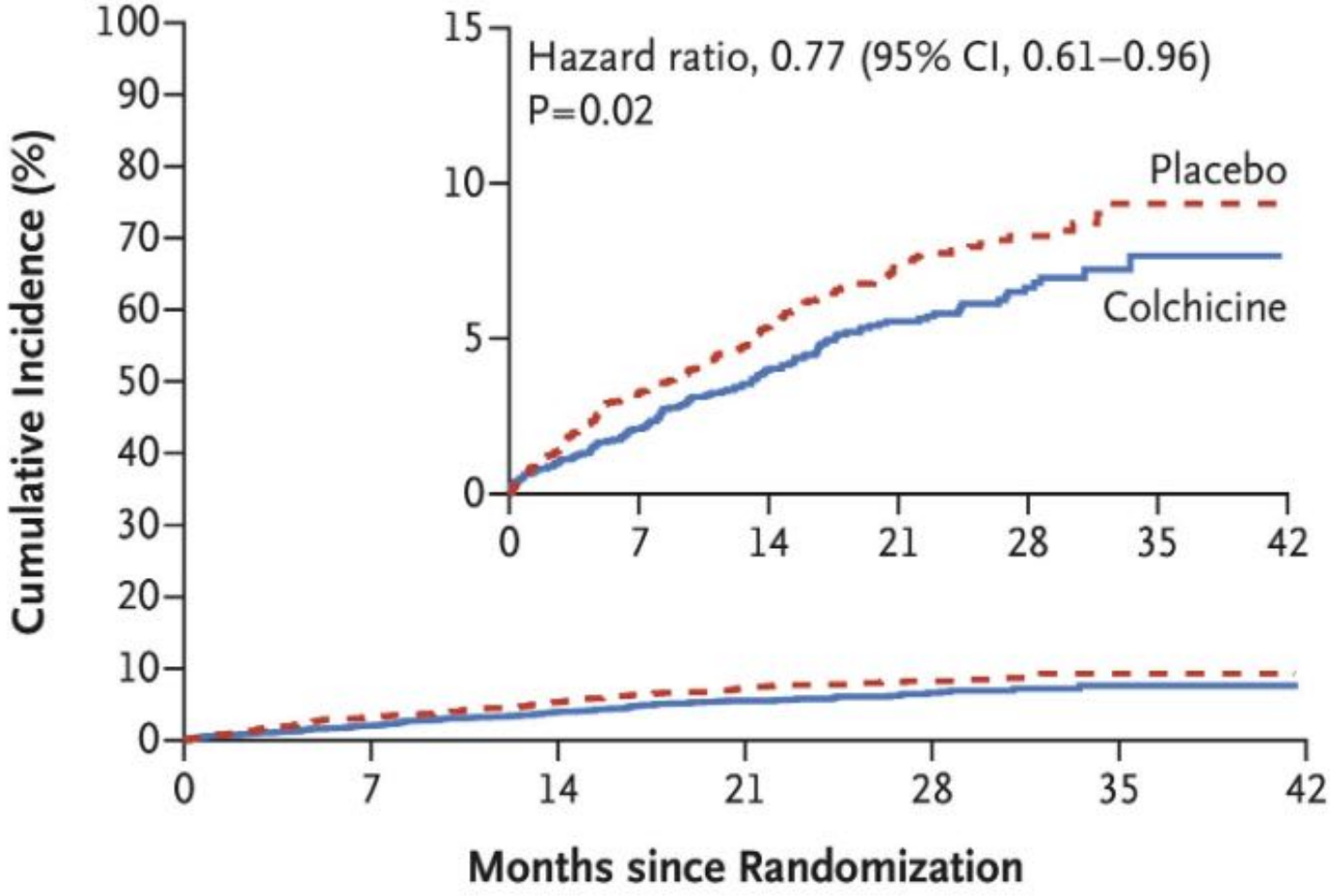


Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

Table S6. Biomarkers of Inflammation.

Biomarker	Colchicine	Placebo
Hs-C reactive protein (mg/L)	N=99	N=108
Randomization, geometric mean (IQR)†	4.27 (2.12, 7.22)	5.09 (2.45, 11.96)
6 months, geometric mean (IQR)	1.37 (0.75, 2.13)	1.60 (0.90, 2.65)
Adjusted GM percent change (95% CI)‡	-70.0 (-74.6, -64.5)	-66.6 (-71.5, -60.8)
Placebo-adjusted GM percent change (95% CI)¶	-10.1 (-28.6, 13.4)	- -
Total white blood cell count ($10^3/\mu L$)	N=992	N=980
Randomization, geometric mean (IQR)†	8.54 (7.10, 10.40)	8.63 (7.20, 10.70)
12 months, geometric mean (IQR)	6.95 (5.99, 8.30)	7.03 (5.96, 8.48)
Adjusted GM percent change (95% CI)‡	-18.81 (-20.12, -17.47)	-19.02 (-20.46, -17.55)
Placebo-adjusted GM percent change (95% CI)¶	0.26 (-2.15, 2.72)	- -

Table 3. Adverse Events (Safety Population).*

Event	Colchicine (N = 2330)	Placebo (N = 2346)	P Value
	number of patients (percent)		
Any related adverse event†	372 (16.0)	371 (15.8)	0.89
Adverse events			
Gastrointestinal event	408 (17.5)	414 (17.6)	0.90
Diarrhea	225 (9.7)	208 (8.9)	0.35
Nausea	43 (1.8)	24 (1.0)	0.02
Flatulence	15 (0.6)	5 (0.2)	0.02
Gastrointestinal hemorrhage	7 (0.3)	5 (0.2)	0.56
Anemia	14 (0.6)	10 (0.4)	0.40
Leukopenia	2 (0.1)	3 (0.1)	0.66
Thrombocytopenia	3 (0.1)	7 (0.3)	0.21
Serious adverse events			
Any serious adverse event‡	383 (16.4)	404 (17.2)	0.47
Gastrointestinal event	46 (2.0)	36 (1.5)	0.25
Infection	51 (2.2)	38 (1.6)	0.15
Pneumonia	21 (0.9)	9 (0.4)	0.03
Septic shock	2 (0.1)	2 (0.1)	0.99
Hospitalization for heart failure	25 (1.1)	17 (0.7)	0.21
Cancer§	43 (1.8)	46 (2.0)	0.77

Limitations:

Withdrew consent and lost to follow-up 0,6% + 1,9%

Stoped the treatment in 18.4% of the colchicine group and in 18.7% in placebo group

Duration of follow-up was relatively short at approximately 23 months.

N= 4745 patients. a larger trial, better assessment

1.6 to 14.4] for placebo). This high percentage of patients discontinuing the trial regimen, combined with unknown end-point status for 2.5% of the patients, could have obscured the true cardiovascular treatment effect or adverse-event profile.

Results apply only to patients who have recently had a myocardial infarction.

CONCLUSIONS

Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo.

to-treat analysis. Regardless, the modest benefit driven by a soft end point of hospitalization for angina and revascularization does not support the routine use of colchicine for secondary prevention